Trends of R&D and Applications in Biomaterials

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상세 내용은 아래와 같습니다:

생체 재료의 연구개발 및 응용기술의 현황

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Hyper-aged society
In Japan

[Graph showing population trends and percentage of old aged men from 1955 to 2055, with a peak in 2055.]
Hyper-aged society

Increasing disturbance of motility: one of three main disease (cancer, circulatory disease (cardiovascular disease), disturbance of motility) for aged persons

Maintenance of QOL by reconstruction of bone function
Increasing demand for high performance implant devices made of metallic biomaterials
Dental Applications

Before correction

After correction

Lip side correction

Tongue side correction

Orthodontic wire and bracket

Attachment post

Porcelain glazed metal crown

Inlay

Crown

Denture

Fig. Examples of dental prostheses
Implant devices made of metallic biomaterials occupy over 70 - 80% of implant devices

Metallic biomaterials for implants are mainly austenitic stainless steels (SUS 316L), Co-Cr alloys, and titanium and its alloys.

Zr based alloys such as Zr-Nb, Zr-Ti, etc.
Titanium and its alloys are getting much attention.

Excellent corrosion resistance
Excellent specific strength: light weight and high strength
Excellent biocompatibility

Table 1 Biocompatibility of various biomaterials judged by patterns of osteogenesis

<table>
<thead>
<tr>
<th>Pattern of osteogenesis</th>
<th>Biomaterials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervened osteogenisis</td>
<td>Stainless steel, Vitallium, PMMA (Polymethyl methacrylate)</td>
</tr>
<tr>
<td>Contact osteogenisis</td>
<td>Titanium, Titanium alloys, Carbon, Alumina, Zirconia, Titania, TiN, Si3N4</td>
</tr>
<tr>
<td>Bonding osteogenisis</td>
<td>Bioglass, Ceravital, Tricalcium phosphate, Hydroxyapatite, A-W glass ceramic</td>
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</tbody>
</table>

General's structural titanium and its alloys were used as biomaterials.

- Pure titanium Grade 1, 2, 3 and 4
  - Purity: Increase (add N, Fe and O)
  - Strength: Increase
  - Ductility: Decrease

- Ti-6Al-4V ELI (ASTM F136-84, F620-87): $\alpha+\beta$ type

- Ti-6Al-4V (ASTM F1108-88): $\alpha+\beta$ type

They are still major titanium biomaterials.
However,

V has been reported to be toxic for human body.

There was an argument on Al being a cause of Alzheimer’s disease.

*Development of titanium alloys composed of nontoxic and allergy-free elements.*

*Development of V-free titanium alloys*

- Ti-6Al-7Nb (ASTM F1295-92, ISO5832-11) (JIS T 7401-3) : \(\alpha + \beta\) type
- Ti-5Al-2.5Fe (ISO5832-10) : \(\alpha + \beta\) type

*Development of V- and Al-free titanium alloys*

- Ti-15Sn-4Nb-2Ta-0.2Pd : \(\alpha + \beta\) type
- Ti-15Zr-4Nb-2Ta-0.2Pd : \(\alpha + \beta\) type (JIS T 7401-5)
- Ti-4.5Al-6Nb-2Fe-2Mo : \(\alpha + \beta\) type, super plastic deformable alloy
However,

Their Young’s moduli are still greater comparing with that of the cortical bone

Development of beta type titanium alloys composed of nontoxic and allergy-free elements with low elastic modulus.

- Ti-13Nb-13Zr (ASTM F1713-96) : near β type, Low modulus
- Ti-12Mo-6Zr-2Fe (ASTM F1813-97): β type, Low modulus
- Ti-15Mo : β type (ASTM F2066) (U.S.A.), Low modulus
- Ti-16Nb-10Hf : β type, Low modulus
- Ti-15Mo-2.8Nb-0.2Si-0.26O : β type, Low, modulus
- Ti-35Nb-7Zr-5Ta (TNZT) : β type, Low modulus
- Ti-29Nb-13Ta-4.6Zr (TNTZ): β type, Low modulus
- Ti-Mo-Sn : β type, Low modulus
- Ti-40Ta, Ti-50Ta : β type, High corrosion resistance
Stress shielding

Conventional high modulus metal implant can induce bone atrophy due to the absence of mechanical stress. It causes refracture after extractive implantation and prosthetic loosening.

Comparison of Young’s moduli of representative metallic biomaterials, bio-polymers, and bone.

Young’s moduli of β-type titanium alloys are much lower than those of α-type and α + β-type titanium alloys.
Development of biologically and mechanically biocompatible titanium alloys

Development of titanium alloys composed of non-toxic- and allergy free- elements with low Young’s modulus and high mechanical properties.

Selection of non-toxic alloying elements:
Avoid to add allergic elements:

Fig. Frequency of nickel sensitization in the population.

Fig. Rate of metallic allergy or each pure metal.

From the view point of cyto-toxicity and allergic problems, Nb, Ta and Zr are judged as the safest elements.

**Ti-Nb-Ta-Zr alloys**

Alloy design using d-electron alloying method

Ti-29Nb-13Ta-4.6Zr referred to as TNTZ
Table: Young’s moduli of α + β type Ti-6Al-4V ELI and Ti-29Nb-13Ta-4.6Zr

<table>
<thead>
<tr>
<th>Material</th>
<th>Young’s modulus (GPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti-6Al-4V ELI (WQ)</td>
<td>110</td>
</tr>
<tr>
<td>Ti-29Nb-13Ta-4.6Zr</td>
<td></td>
</tr>
<tr>
<td>• WQ</td>
<td>63</td>
</tr>
<tr>
<td>• WQ + aged at 673 K for 3.6 k</td>
<td>97</td>
</tr>
<tr>
<td>• WQ + CW</td>
<td>55 - 60</td>
</tr>
<tr>
<td>Cortical bone</td>
<td>10 - 30</td>
</tr>
</tbody>
</table>

WQ: Water quenching after solution treatment
AC: Air cooling after solution treatment
CW: Cold working

Processing for Improving fatigue strength

(a) Process A

(b) Process B

Fig.: Schematic drawings of thermomechanical processings. (a) process A and (b) process B, for Ti 29Nb 13Ta 4.6Zr. ST, WQ and CRR indicate solution treatment, water quenching and cold rolling ratio, respectively.
S-N curves of Ti-29Nb-13Ta-4.6 in as-solutionized conditions (TNTZ<sub>ST</sub>) and as-cold rolled conditions (TNTZ<sub>CR</sub>) and TNTZ<sub>ST</sub> and TNTZ<sub>CR</sub> conducted with aging at 598 K, 673 K and 723 K for 259.2 ks with those of Ti-6Al-4V ELI in air.

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**Evaluation of cyto-toxicity of Ti-29Nb-13Ta-4.6Zr**

**Cyto-toxicity tests**

**Extraction of test solution**
- Rotation speed: 60rpm
- Extraction period: 7days, 14days

**Filtration of extracted solution**
- Non-filtrated solution (Including wear debris)
- Filtrated solution

**Evaluation of cyto-toxicity**
- L-929 cell
- Exposure period: 2days
Figure: Cell viability of L-929 in (a) non-filtrated and (b) filtrated cultivate solutions evaluated by MTT method for pure titanium, Ti-6Al-4V ELI and Ti-29Nb-13Ta-4.6Zr.

Animal experiment for bone healing and remodeling

Implanted rod made of Ti-29Nb-13Ta-4.6Zr, Ti-6Al-4V ELI or stainless steel (SUS316L) into intramedullary canal of rabbit

Artificial tibial fracture

C.M.R. of cross section at 24 weeks

(i) Ti-29Nb-13Ta-4.6Zr alloy (60 GPa)
(ii) Ti-6Al-4V ELI alloy (110 GPa)
(iii) SUS 316L stainless steel (160 GPa)
Based on the design of AO mini DCP for human finger, the bone plate were made of TNTZ.

The plate and screws of Ti-6Al-4V and SUS316L were also provided as control.

As experimental animal, mature New Zealand white rabbits (all male, weight about 3kg) were used.

**X-ray follow-up**

Under sedation, X-ray observation was made in lateral and AP views.
CMR observation

At 48 weeks after the fixation, both tibiae were extracted with the bone plate, and stained by Fuchsine, then embedded in PMMA.

Thin slice specimens of 130 μm at 3 levels of the bone plate were made for CMR observation.

X-ray follow-up: SUS316L

The thinning of cortical bone begun from 7 weeks, and the cortical bone is almost disappeared at 12 weeks after the fixation.
X-ray follow-up: Ti-6Al-4V

The thinning of cortical bone begun from 7 weeks, and the cortical bone is almost disappeared at 14 weeks after the fixation.

X-ray follow-up: TNTZ

The thinning of cortical bone begun from 10 weeks, and the cortical bone is almost disappeared at 18 weeks after the fixation.
X-ray images at 48 w

SUS316L
In X-ray at 48 weeks, the bone tissue under the bone plate was almost disappeared, there was no significant difference among SUS316L, Ti-6Al-4V and TNTZ.

CMR at 48w : SUS316L
Thinning of cortical bone is observed in all levels.

In middle level, cortical bone is entirely changed in porous bone.

In distal level, porous bone is observed under the bone plate.
CMR at 48w : Ti-6Al-4V

Thinning of cortical bone is observed in all levels.

In middle level, poor bone tissue is observed under the bone plate.

In distal level, porous bone is observed under the bone plate.

CMR at 48w : TNTZ

Thinning of cortical bone is observed in all levels.

Porous bone is observed under the bone plate in proximal level.

The diameter of the tibia bone is increased, where thin bone tissue is observed in the medullary cavity.
Increase of tibia diameter in TNTZ

The double wall structure is observed with different X-P densities and a clear boundary line at the middle and distal levels.

Increase of tibia diameter in TNTZ

The shape of the inner wall is close to the original cortical bone.

The outer wall seems to be newly formed cortical bone.

The inner wall seems to be the remains of old cortical bone.
Further decreasing Young’s modulus:

Anisotropy of deformation of β-type Ti-Nb-Ta-Zr system alloy is very strong.

Single crystal biomaterial of β-type Ti-Nb-Ta-Zr system alloy

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Fig. Relationships between strain measured with strain gage and strain of lattice calculated using by several diffraction angles of TNTZ_{20} and S45C.

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Fig. Relationship between Young’s modulus and crystal orientation of TNTZ.

Young’s modulus is the smallest to be 35 GPa at a direction of <100>.

This Young’s modulus is almost equal to that of the cortical bone, which is 10-30 GPa.

Creation of single crystal biomaterial

Fig. X-ray diffraction patterns of TNTZ$_{ST}$ and TNTZ$_{CR10-90}$ on rolling plane.
Simple method for further decreasing Young’s modulus: porous titanium and its alloys

![Graph showing relationship between Young’s modulus and porosity in porous titanium.](image1)

**Fig. Relationship between Young's modulus and porosity in porous titanium**

![Graph showing relationship between strength and porosity in porous titanium.](image2)

**Fig. Relationship between strength and porosity in porous titanium.**

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**Bio-functional porous titanium and PMMA composites**

1. MMA solution mixed with AIBN powder
2. Glass tube
3. Vacuum desiccator
4. Bath
5. Water
6. Heater
7. Heater
8. Heater
9. Porous pure titanium
10. 2) A porous pure titanium is placed in the glass tube.
11. 3) Air bubbles in the pores of the porous pure titanium is removed in a chamber under a reduced pressure.
12. 4) The MMA solution is polymerized in a water bath at a constant temperature.
13. 5) The porous pure titanium/PMMA composite is taken out from the glass tube.
14. 6) Extra part of PMMA is removed from the porous pure titanium/PMMA composite by machining mechanically.
Almost 100% pores are filled with PMMA

Tensile strengths of pTi and pTi/PMMA composite

Effect of PMMA filling on improvement of tensile strength appear in porosity range over 40%

Fig. Tensile strength of pTi and pTi/PMMA composite as a function of porosity.
Young’s moduli of pTi and pTi/PMMA composite

PMMA filling does not significantly affect the value of Young’s modulus of pTi

Fig. Young’s modulus of pTi and pTi/PMMA composite as a function of porosity.

Development of spinal implant rods made of TNTZ

Spinal Fusion
Animal Experiment

Two ovine were used in this study.
One intervertebral fixation was conducted by connecting 4 pedicle screws and 2 rods with 4 plugs.

radios : TNTZ
plugs and screws: 6-4Ti

Radiographs evaluation

- There was no evidence of movement of the screw or rod systems.
- There was no evidence of excessive bony response at the implant site.
- There was no evidence of device fracture or failure.
Histological observation

Pic. The micrograph of hematoxylin and eosin (HE) stained section of the surrounding rod part

Further development of biocompatibility is required because metallic biomaterials are not bioactive.

Surface modification using phosphate calcium is highly advantageous.
Bioactive ceramic (hydroxyapatite) modification

(1) Dry process
   Plasma spray coating
   Ion plating
   Pulse laser evaporation
   RF magnetron sputtering
   Dynamic mixing
   Metal organic chemical vapor deposition (MOCVD)
   Super plastic bonding
   Ca ion mixing

(2) Wet process
   Alkaline treatment process
   Electro-chemical treatment process

(3) Dip coating
   Calcium phosphate glass coating process

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Various processing for fabricating calcium phosphate films

Fig. Comparison of adherence and coating area of different methods.
Fig. Typical XRD patterns of (a) TNTZ_{ST}, (b) TNTZ_{HAp}, and (c) TNTZ_{α-TCP}. Deposition time is 15 min.

Fig. 6 SEM microstructure of Ca-P-O films (T_{sub} = 973K, P_{tot} = 0.8kPa.)
(a), (b) T_{prec}(Ca(dpm))_2 = 568K, T_{prec}((C_6H_5O)_3PO) = 493K
(c), (d) T_{prec}(Ca(dpm))_2 = 543K, T_{prec}((C_6H_5O)_3PO) = 513K
Fig. SEM images of surfaces on TNTZ: (a) TNTZ_{ST} and (b) TNTZ_{HAP} before immersion tests, and (c) TNTZ_{ST} and (d) TNTZ_{HAP} after immersion tests.
Cross-sectional SEM micrographs of glass-ceramic-coated TNTZ after 1-year implantation.

Creating multifunctionalities; super elasticity and shape memory effect:

Insertion of stent from femoral artery to coronary artery

: Treatment in blood vessel

TiNi shape memory alloy
Ni is high risk element for allergy.

Ni free shape memory / super elastic titanium alloys for biomedical applications.

Ni free β type titanium alloys showing super elastic and/or shape memory effect is required.

Peculiar elastic deformation behavior (psuedo elastic)
in Ti-30Nb-10Ta-5Zr: around 3% total psuedo elastic strain

Fig. Loading-unloading stress-strain curves of Ti-(a) 27.2Nb, (b) 27.9Nb, (c) 28.7Nb, and (d) 30.3Nb-13Ta-4.6Zr
Processing for making super elastic wire from ingot making TNTZ

- Cold Rolled TNTZ
  - Cross Section (10 mm x 10 mm)
  - Softening
    - Diameter (φ 10 mm)
  - Several Times
  - Diameter (φ 1.0 mm)
  - Diameter (φ 0.3 mm)
  - 1073 K, 0.3 ks
  - TNTZ_{0.1}(φ 1.0 mm)
  - TNTZ_{0.3}(φ 0.3 mm)

Fig. Schematic drawing of thermomechanical processing for Ti-29Nb-13Ta-4.6Zr (TNTZ).

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- Maximum elastic strain ≈ 2.9%
- Stress-strain curves of as-cold drawn TNTZ(φ0.3mm).
  - W.R. indicates work ratio.

Fig. Stress-strain curves of as-cold drawn TNTZ(φ0.3mm).
Dental Applications

Before correction

Lip side correction

After correction

Tongue side correction

Orthodontic wire and bracket

Surgical wire

Manufacturing Process
Surgical wire

Thank you very much for your attention!